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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/016,743	01/30/98	ROSENBLATT J	176/60192(UR

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MICHAEL L GOLDMAN ESQ
NIXON PEABODY LLP
CLINTON SQUARE
P O BOX 1051
ROCHESTER NY 14603

EXAMINER	
HELMS,L	

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 02/09/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/016,743	Rosenblatt et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☒ Responsive to communication(s) filed on *20 Dec 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is clos d** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-76* is/are pending in the applicat

Of the above, claim(s) *11-24 and 26-76* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-10 and 25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3,4,and 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-10 and 25, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that "all groups of the invention identified in the written restriction requirement are closely related and, therefore, would require common areas of search and consideration." This is not persuasive. Applicant has provided no evidence to establish why the requirement for restriction is improper. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Upon reconsideration, the election of species required in paper #9 mailed 9/28/99 is not required and is withdrawn.

3. Claims 11-24 and 26-76 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

4. This application contains claims 11-24 and 26-76 drawn to an invention nonelected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Claims 1-76 are pending.

Claims 1-10 and 25 are under examination.

Drawings

6. The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

a. Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(I), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

b. Figures 4, 5, 12, 14, 15, 17, 18, and 19 need to be labeled separately, for example, Figure 4A, Figure 4B, Figure 4C, etc.

Specification

7. The disclosure is objected to because of the following informalities:

a. The brief description of the drawings (on page 9) needs to include views labeled separately for Figure 5, for example.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-10 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-10 and 25 are indefinite for reciting "associated with" in claim 1 for the exact meaning of the phrase is not known. It is not clear if the term "associate" is intended to encompass covalent as well as non-covalent interactions. Is the term intended to mean the polypeptides are in the same test tube, aggregated, or dimerized by ionic or hydrogen bonds? As written, it is impossible to determine the metes and bounds of the claimed invention.

b. Claim 2 recites the limitation "tumor associated antigen" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

c. Claim 6 is indefinite as being structured as an improper Markush claims, by recited "... PF-4, and RANTES or an active fragment thereof.". (See MPEP 2173.05(h)). Proper Markush claims are in the format of "X is selected from a group consisting of A, B, C, and D," or "the X is A, B, C or D". In addition, is unclear if it is intended that the "active fragment thereof" is directed to RANTES or others listed in the group.

d. Claims 1-10 and 25 are indefinite for reciting "chemokine active fragment" for the exact meaning of the phrase is not known. It is not clear what activity is retained in a fragment of a chemokine. As written, it is impossible to determine the metes and bounds of the claimed invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-10, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric molecule comprising a binding domain which is an antibody or fragment thereof which specifically binds to the tumor associated antigen and a chemokine, does not reasonably provide enablement for a chimeric molecule comprising any binding domain and a chemokine active fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims are broadly drawn to a chimeric molecule comprising any binding domain and a chemokine active fragment.

c. The specification teaches chimeric molecules comprising a binding domains of antibodies or fragments that retain antigen binding and chemokines (see Examples 1-10). The specification fails to enable binding domains other than antibodies or antigen binding fragments and chemokine active fragments.

d. The claims are broadly drawn to any binding domain, however, antibodies are known in the art to be highly specific and have high affinity for the antigen. One skilled in the art would reasonably conclude that molecules other than antibodies would not be specific and have such binding affinity as antibodies. The claims also are drawn to chemokine active fragments, however, the specification does not enable or teach what fragments of chemokines would be active.

e. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

f. Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human

insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

g. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

h. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results.

I. In view of the unpredictability in the art as evidenced by Burgess et al , Lazar et alm, Schwartz et al, and Lin et al, and the lack of guidance and lack of examples with regard to producing a chemokine active fragment or binding domain other than an antibody domain encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

j. Amending the claims by moving claim 2 into independent claim 1 and removing the term "or active fragment thereof" would be sufficient to obviate this rejection.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-2, 5-6, 8, 10, and 25 are rejected under 35 U.S.C. 102(a) as being anticipated by Holzer et al (Cytokine 8:214-221, March 1996) .

DRoP

a. The claims recite a chimeric molecule comprising a binding domain capable of specifically binding to a tumor cell associated antigen and a chemokine which is associated with the binding domain such that the binding domain remains capable of binding to the tumor cell associated antigen and the chemokine retains activity. Further the binding domain is an antibody or fragment thereof which specifically binds the antigen, the chimeric molecule comprises a flexible linker connecting the chemokine and the binding domain, the chemokine is IL-8, the tumor specific antigen is from breast cancer cells, the antigen is a cell surface antigen, and a composition comprising the chimeric molecule and a carrier.

b. Holzer et al teach a fusion protein comprising an antibody to the EGF receptor, which is a tumor cell surface antigen expressed on breast cancer cells, (see abstract and page 215, left column 2nd paragraph) and the chemokine IL-8 that retains its activity (see page 216, binding of

Fab-Il-8 to IL-8 receptor). The construct comprises the antibody and a linker connecting the domains (see page 215, Results) and compositions of the chimeric molecules in PBS (see page 219, top right column). The recitation of the intended use of "stimulating a tumor specific immuno response" is given no patentable weight in this rejection. Therefore, the reference reads on the claims.

14. Claims 1-2, 5-8, 10, and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Holzer et al et al (U.S. Patent 5,824,782, filed 9/15/95).

a. Claims 1-2, 5-6, 8, 10, and 25 have been described supra. Claim 7 recites the chemokine is RANTES.

b. Holzer et al teach a fusion protein comprising an antibody to the EGF receptor, which is a tumor cell surface antigen expressed on breast cancer cells, (see abstract and column 1, lines 1-15) and the chemokine IL-8 that retains its activity (see column 6, lines 52-59). The construct comprises the antibody and a linker connecting the domains (see column 4, lines 55-56) and compositions of the chimeric molecules in PBS (see column 5, line 25, and column 8, lines 49-50). Holzer et al also teach the chemokine RANTES (see column 2, lines 37-40). The recitation of the intended use of "stimulating a tumor specific immuno response" is given no patentable weight in this rejection. Therefore, the reference reads on the claims.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holzer et al (U.S. Patent 5,824,782, filed 9/15/95) and further in view of Bacus (U.S. Patent 5,514,554, filed 10/7/93).

a. The claim recites a chimeric molecule comprising a binding domain capable of specifically binding to her2/neu and a chemokine which is associated with the binding domain such that the binding domain remains capable of binding to the tumor cell associated antigen and the chemokine retains activity.

b. Holzer et al has been discussed supra. Holzer et al does not teach specifically a binding domain that specifically binds to her2/neu. This deficiency is made up in the teachings of Bacus.

c. Bacus teach monoclonal antibodies to her2/neu (see abstract).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds her2/neu as taught by Bacus and a chemokine as taught by Holzer et al.

e. One of ordinary skill in the art would have been motivated to produce the claimed invention because Holzer et al teach "new fusion proteins which consist of a tumor-associated targeting element, preferably a monoclonal antibody or a fragment thereof, recognizing and specific for a molecule which is preferentially expressed on tumor cells... and a biologically active ligand selected from the group of chemokine proteins....can be used in tumor therapy and diagnostics." (See column 1, lines 1-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Bacus teach the antibodies to her2/neu

can be used alone or linked to conjugates which can be used as therapeutic agents (see column 4, lines 10-15).

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Holzer et al teach "fusion proteins according to the invention... could in fact cause chemotactic activity" (see column 7, lines 13-16). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Bacus teach the antibodies of the present invention are specific for the her2/neu product and significantly inhibit the tumorigenic growth of her2 cells. (See column 3, lines 59-67).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holzer et al (U.S. Patent 5,824,782, filed 9/15/95) and further in view of Huston et al (Meth. Enzymol. 203:46-88, 1991).

a. Claims 1 and 2 have been described supra. Claims 3 and 4 recite wherein the chemokine or active fragment is linked to the amino terminus of the heavy chain of the antibody.

b. Holzer et al has been described supra.

c. Huston et al teach Fusion proteins with the effector fused at the amino terminal of the heavy chain of the antibody (see pages 55-59 and Figure 3A).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have made a construct comprising a binding domain which specifically binds to a tumor cell associated antigen and a chemokine fusion as taught by Holzer et al with the chemokine linked to the amino terminus of the heavy chain as taught by Huston et al.

e. One of ordinary skill in the art would have been motivated to produce the claimed invention because Holzer et al teach "new fusion proteins which consist of a tumor-associated targeting element, preferably a monoclonal antibody or a fragment thereof, recognizing and specific for a molecule which is preferentially expressed on tumor cells... and a biologically active ligand selected from the group of chemokine proteins....can be used in tumor therapy and diagnostics." (See column 1, lines 1-15). In addition, one of ordinary skill in the art would have been motivated to produce the claimed invention because Huston et al teach "sFv analogs suggested that VL or VH domain, respectively in each orientation, would tolerate amino-terminal fusion" (see page 57, first full paragraph).

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention because Holzer et al teach "fusion proteins according to the invention... could in fact cause chemotactic activity" (see column 7, lines 13-16). In addition, one of ordinary skill in the art would have had a reasonable expectation of success because Huston et al teach "Investigations have demonstrated that protein effector domains can be successfully fused to the amino terminus of the sFv." (See page 57, second full paragraph).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

JULIE BURKE
PRIMARY EXAMINER